UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,505	04/06/2001	Eyal Raz	UCAL-203	6822

7590 06/02/2004

Carol L. Francis
BOZICEVIC, FIELD & FRANCIS LLP
Suite 200
200 Middlefield Road
Menlo Park, CA 94025

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,505	RAZ ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7,10,14,20,21 and 27-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34,35 and 37-39* is/are allowed.

6)☒ Claim(s) *4,7,10,14,20,21,27,29-33,36 and 40-47* is/are rejected.

7)☒ Claim(s) *3 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 3/11/24 has been entered.

Amended claims 3-4, 7, 10, 14, 20-21 and 27-47 are pending in the present application and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 41-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing a Th2 immune response to a plant allergen in a mammalian subject, the method comprising administering to the mammalian subject an effective amount of the composition of claim 27 to reduce a Th2 immune response to the plant allergen, wherein the immunomodulatory nucleic acid comprising **an unmethylated** 5'—cytosine-guanine-3' sequence, does not reasonably provide enablement for a method for reducing a Th2 immune response to a plant allergen in a mammalian subject, the method comprising administering to the mammalian subject an effective amount of the composition of claim 27 to reduce a Th2 immune response to the plant allergen, wherein the immunomodulatory nucleic acid simply comprising the sequence 5'-cytosine-guanine-3' (including both methylated and unmethylated 5'-cytosine-guanine-3' sequence). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention commensurate in scope with these claims. **This is a new ground of rejection necessitated by Applicants' amendment.**

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for a broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. The claims encompass a method for reducing a Th2 immune response to a plant allergen in a mammalian subject, the method comprising administering to the mammalian subject an effective amount of the composition of claim 27 to reduce a Th2 immune response to the plant allergen, wherein the immunomodulatory nucleic acid simply comprising the sequence 5'-cytosine-guanine-3' (including both methylated and unmethylated 5'-cytosine-guanine-3' sequence due to the open language of the term "comprising").

(b) The state and the unpredictability of the prior art. At the effective filing date of the present application (4/7/2000), it is well established that there is a definite requirement for **unmethylated CpG motifs** in bacterial DNA, plasmid vectors and synthetic oligonucleotides to induce B-cell activation, natural killer cell (NK) lytic activity and antigen specific immunity, including the induction of Th-1 type immune responses,

as evidenced by the teachings of Krieg et al. (WO 96/02555), Krieg et al. (WO 98/18810) and Carson et al. (WO 98/16247). It should also be noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

(c) The amount of direction or guidance presented. Apart from the exemplification showing that upon co-administration of the immunostimulatory sequence of SEQ ID NO:1 containing the AACGTT motif with the plasmid pNDKm/hssHAΔ36Amb a1 encoding a ragweed allergen into mice that were sensitized to Amb a1, a significant reduction of Amb a1-specific IgE was obtained at week 8 following subsequent challenges (example 6), the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a similar reduced Amb a1-specific IgE and/or a shift in the immune response in any mammalian subject, wherein the immunostimulatory sequence simply "comprising" the sequence 5'-cytosine-guanine-3", which encompasses the methylated and unmethylated CpG sequences. There is no evidence of record indicating or suggesting that any immunomodulatory nucleic acid containing methylated CpG motifs could still possess the desired immunomodulatory activity, for this instance to reduce specifically a Th2 immune response to a plant allergen. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Otherwise, with the lack of sufficient guidance provided by this disclosure, and in light with the state of the prior art as discussed above, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Additionally, as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art, particularly with the ability of methylated CpG sequence to induce the desired immune responses, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 10, 14, 20-21, 29, 33 and 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

Claim 10 and its dependent claims are vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtain a "derivative" of a signal sequence. The term implies a number

of different steps that may or may not result in a change in the functional characteristics of a signal sequence from the source that it is "derived from". It is unclear how closely related to the starting material the "derivative" is? It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of acquiring the plant allergen and/or signal sequence.

Claims 4, 29 and 46 recites the limitation "a wild type sequence of the non-host species" in lines 2-3 of the claims. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any non-host species in claims 36, 27 and 10 from which claims 4, 29 and 46 are respectively dependent. The metes and bounds of the claims are not clearly determined. Additionally, it is unclear what is the relationship or connection between the non-host species or a host species with the nucleic acid encoding a plant allergen? Doesn't a plant belong to a plant phylum or plant kingdom? Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7, 10, 14, 27, 30, 33, 36, 40-43 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Caplan (US 2003/0035810 with the effective filing date of 4/6/2000). **This is a new ground of rejection.**

Caplan teaches methods and compositions for treating allergic responses in subjects who are allergic to allergens or susceptible to allergies. Caplan teaches specifically the use of genetically modified microorganisms to express and deliver allergens to a subject therefore reduces the exposure of the allergens to the subject's IgE antibodies, which lead to allergic reactions and possibly anaphylaxis, and that microorganisms may act as a natural adjuvant to enhance desirable Th1-type immune responses (see Summary of the Invention). Any allergen may be produced by microorganisms, including weed pollens (Amb a 1-7), grass pollens, tree pollens, protein allergens found in nuts, legumes and many others (page 7, paragraphs 0062-0068 and page 14 of Appendix A). Caplan also teaches that in a preferred embodiment secretion signals such as those found in hemolysin and listeriolysin, specifically HlyA signal peptide from *E.Coli*, are used to form fusion proteins containing allergic polypeptides (page 6, paragraphs 0055-0061, particularly paragraph 0060). Caplan further teaches that larger amounts of polypeptides are useful for inducing Th1 responses (paragraph 0070), and that the compositions include adjuvants and immunomodulatory polypeptides or immunostimulatory factors (paragraph 0073), including oligonucleotides containing CpG motifs (paragraph 0075), microbial extracts such as fixed *Staphylococcus auresus, Mycobacterium tuberculosis, Streptococcal*

preparations that induce Th1-type responses and not Th2-type response (These would qualify as a universal antigen, paragraph 0078).

Due to the open language of the term "comprising" recited in the instant claims, the polynucleotide composition of the presently claimed invention can also be present in the form of genetically modified microorganisms taught by Caplan. Therefore, these instant claims read over the compositions and methods taught by Caplan and thus Caplan anticipates the instant claims.

Amended claims 27 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. (U.S. Patent No 5,965,455) as evidenced by Schultz et al. (Gene 54:113-123, 1987). **This is a new ground of rejection necessitated by Applicants' amendment.**

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells as well as yeast cells (see col. 11, lines 1-20). It is also noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as

well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors for expression in yeast cells include the vector taught by Schultz et al. disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph).

As an immunomodulatory nucleic acid comprising the sequence 5'-cytosince-guanine-3 in the amended claim 27 can be present in a polynucleotide comprising a nucleic acid molecule encoding a plant allergen (no longer as a separate immunomodulatory nucleic acid molecule), the nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments that are disclosed by Singh et al. also contain CpG sequences (see Figs. 3b-1, 3b-2, 3c; Figs. 10a-1, 10a-2, 10b-1, 10b-2, for examples).

Accordingly, the teachings of Singh et al. meet all the limitation of the instant claim as evidenced by Schulz et al. Therefore, Singh et al. anticipate the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 20-21, 27, 31-32, 41 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan (US 2003/0035810 with the effective filing date of 4/6/2000) in view of Carson et al. (WO 98/16247, IDS). **This is a new ground of rejection.**

Caplan teaches methods and compositions for treating allergic responses in subjects who are allergic to allergens or susceptible to allergies. Caplan teaches specifically the use of genetically modified microorganisms to express and deliver allergens to a subject therefore reduces the exposure of the allergens to the subject's IgE antibodies, which lead to allergic reactions and possibly anaphylaxis, and that microorganisms may act as a natural adjuvant to enhance desirable Th1-type immune responses (see Summary of the Invention). Any allergen may be produced by microorganisms, including weed pollens (Amb a 1-7), grass pollens, tree pollens, protein allergens found in nuts, legumes and many others (page 7, paragraphs 0062-0068 and page 14 of Appendix A). Caplan also teaches that in a preferred embodiment

secretion signals such as those found in hemolysin and listeriolysin, specifically HlyA signal peptide from *E.Coli*, are used to form fusion proteins containing allergic polypeptides (page 6, paragraphs 0055-0061, particularly paragraph 0060). Caplan further teaches that larger amounts of polypeptides are useful for inducing Th1 responses (paragraph 0070), and that the compositions include adjuvants and immunomodulatory polypeptides or immunostimulatory factors (paragraph 0073), including oligonucleotides containing CpG motifs (paragraph 0075), microbial extracts such as fixed *Staphylococcus auresus, Mycobacterium tuberculosis, Streptococcal* preparations that induce Th1-type responses and not Th2-type response (These would qualify as a universal antigen, paragraph 0078).

Caplan does not specifically teach methods and compositions containing oligonucleotides comprising CpG motifs having the selected nucleotide sequences, and specifically having the sequence AACGTT.

However, at the effective filing date of the present application Carson et al. already disclosed various CpG motifs, including those recited by the instant claims (page 4, lines 18-23; page 15, line 20 continues to line 17 of page 16) that are useful for the induction of Th1-type immune responses.

Accordingly, it would have been obvious for an ordinary skilled artisan to use the CpG motifs containing oligonucleotides taught by Carson et al. in the methods and compositions disclosed by Caplan.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the CpG motifs-containing oligonucleotides taught by Carson et

al. have been shown to be useful for the induction of Th1 responses (paragraph 0070) which are beneficial for treating allergies.

One of ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Caplan and Carson et al., coupled with a high level of skill of an ordinary skilled artisan in the art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 4, 10, 27, 29, 36 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan (US 2003/0035810 with the effective filing date of 4/6/2000) in view of Kim et al. (Gene 199: 293-301, 1997; IDS). **This is a new ground of rejection.**

The teachings of Caplan have been disclosed above.

Caplan does not specifically teach methods and compositions containing a polynucleotide wherein at least one codon of the nucleic acid encoding the plant allergen is modified from a wild-type sequence to an analogous codon of a host species.

At the effective filing date of the present application, Kim et al. already teach that the choice of synonymous codons in many species is strongly biased and that a correlation exists between high expression and the use of selective codons in a given organism (page 294, col. 1, first sentence of second paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the nucleic acid sequences encoding plant allegens taught by Caplan by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used in microorganisms to be genetically modified in order to increase expression efficiency of the plant allergens.

One of ordinary skilled artisan would have been motivated to carry out the above modification in order to obtain an efficient and high level of expression of recombinant plant allergens in genetically modified microorganisms to be administered into a subject in need thereof, particularly Caplan also teaches that larger amounts of polypeptides are useful for inducing Th1 responses (paragraph 0070) which are beneficial for treating allergies.

One of ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Caplan and Kim et al., coupled with a high level of skill of an ordinary skilled artisan in the art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 27 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rogers et al. (U.S. 5,776,761) in view of Singh et al. (U.S. Patent No 5,965,455), Schultz et al. (Gene 54:113-123, 1987). **This is a new ground of rejection necessitated by Applicants' amendment.**

Rogers et al. already disclose cDNAs encoding Amb al allergic proteins or peptides (do not contain native signal peptide) from ragweed, and teach techniques to clone as well as produce the allergic protein or peptide in cultured transforming host cells (see abstract, col. 19, lines 36-52). As an immunomodulatory nucleic acid comprising the sequence 5'-cytosince-guanine-3 in the amended claim 27 can be present in a polynucleotide comprising a nucleic acid molecule encoding a plant allergen, it is noted that the nucleic acid sequences coding for Amb a1 allergen proteins or peptides that are disclosed by Rogers et al. also contain CpG sequences, including the sequence AACGTT (see Figs. 2-4, 11-15, for examples; particularly Fig. 11B, nucleotides 770-790 contains the sequence AACGTT).

Rogers et al. do not specifically teach to the preparation of nucleic acid sequences coding for Amb a1 allergic proteins or peptides, and wherein such nucleic acids contain a heterologous signal sequence.

However, at the effective filing date of the present application, Singh et al. already disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Specifically, Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be expressed and purified from host cells (mammalian and yeast cells) as well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors

for expression in yeast cells including and not limited to the vector taught by Schultz et al. disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph). Schulz et al. further teach that the *S. cerevisiae* yeast system has been used for the expression, in biologically active form, of medically significant proteins such as vaccines and therapeutic agents. In particularly, the signals for the post-translational addition of core oligosaccharides are similar in yeast and eukaryotic cells, and heterologous proteins are specifically N- or O-glycosylated (page 114, bottom of col. 1).

Accordingly, it would have been obvious for an ordinary skilled artisan to clone and express the nucleic acid sequences encoding Amb al allergic proteins or peptides of Rogers et al. in a yeast expression system taught by Singh et al and Schulz for the preparation of Amb a1 allergic proteins or peptides to desensitize an individual in need of treatment as contemplated by Rogers et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the *S. cerevisiae* yeast system has been used for the expression, in biologically active form, of medically significant proteins such as vaccines and therapeutic agents as taught by Schultz, and that the same system has been taught by Singh et al. to express rye grass pollen allergens.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Rogers et al., Singh et al. and Schultz et al., coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (U.S. Patent No 5,965,455) as evidenced by Schultz et al. (Gene 54:113-123, 1987) and in view of Kim et al. (Gene 199: 293-301, 1997; IDS). **This is a new ground of rejection necessitated by Applicants' amendment.**

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells as well as yeast cells (see col. 11, lines 1-20). It is also noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as well as from the cell culture medium (col. 12, lines 6-8). Singh et al. specifically teach suitable vectors for expression in yeast cells include the vector taught by Schultz et al.

disclosed in Gene 54:113-123, 1987(col. 11, lines 18-21). The yeast expression vector (pYEBVC-1) utilized by Schultz for expressing a 400-kDa envelope glycoprotein into the culture fluids of JRY188 transformants contain a yeast MFα1 promoter and pre-pro-leader polypeptide (page 115, col. 1, top of last paragraph). As an immunomodulatory nucleic acid comprising the sequence 5'-cytosince-guanine-3 in the amended claim 27 can be present in a polynucleotide comprising a nucleic acid molecule encoding a plant allergen, it is noted that the nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments that are disclosed by Singh et al. also contain CpG sequences (see Figs. 3b-1, 3b-2, 3c; Figs. 10a-1, 10a-2, 10b-1, 10b-2, for examples).

Singh et al. do not specifically teach the preparation of nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and their peptide fragments, wherein at least one codon of the nucleic acid sequences encoding the allergic antigens is modified to an analogous codon of a host species.

At the effective filing date of the present application, Kim et al. already teach that the choice of synonymous codons in many species is strongly biased and that a correlation exists between high expression and the use of selective codons in a given organism (page 294, col. 1, first sentence of second paragraph). Additionally, Kim et al. disclose non-random codon-usage patterns in highly expressed human and yeast genes (Figure 1).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the nucleic acid sequences encoding ryegrass pollen allergen Lol p Ib family members

of Singh et al. by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used in a given selected expression host cell (e.g., mammalian cells or yeast cells) in order to increase expression efficiency.

One of ordinary skilled artisan would have been motivated to carry out the above modification in order to obtain an efficient and high level of expression of recombinant ryegrass pollen allergens in any given host cells, for example in yeast cells, in light of the teachings of Kim et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Rogers et al., Singh et al. and Schultz et al., coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

The modified nucleic acids as a result of the combined teachings of Singh et al., Schultz et al. (Gene 54:113-123, 1987), and Kim et al. are indistinguishable from the polynucleotide composition of the instantly claimed invention.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claims 34-35 and 37-39 are allowed.

Claims 3 and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER